

Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Error
11	BRS	L11	326	heparin adj cofactor adj II	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:10		0
12	BRS	L12	153	protein adj c adj inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:12		0
13	BRS	L13	1386	platelet adj factor\$14	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:13		0
14	BRS	L14	225	bovine adj pancreatic adj trypsin adj inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:14		0
15	BRS	L15	6	ghilanten\$1related adj inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:15		0
16	BRS	L16	18	7 same (8 or 9 or 10 or 11 or 12 or 13 or 14 or 15)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:17		0
17	BRS	L17	0	16 same 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:16		0
18	BRS	L18	0	7 same 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:17		0
19	BRS	L19	177	heparin\$1binding adj domain	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:17		0
20	BRS	L20	8	19 same (8 or 9 or 10 or 11 or 12 or 13 or 14 or 15)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:17		0
21	BRS	L21	0	20 same 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/0 9 07:17		0

Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error or Definition	Errors
1 BRS	L1	4	((TFPI or TFPI-2) same ((kunitz same (domain adj TFPI)) or (kunitz same (domain adj TFPI-2)))) same (chimeric or fusion)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:06			0
2 BRS	L2	407	TFPI	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:06			0
3 BRS	L3	50	TFPI-2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:06			0
4 BRS	L4	42	2 same 3 same kunitz same domain	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:07			0
5 BRS	L5	24473	(chimeric or fusion) adj protein	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:08			0
6 BRS	L6	9	4 same 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:08			0
7 BRS	L7	315	heparin adj binding adj domain	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:16			0
8 BRS	L8	343	protease adj nexin\$1	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:09			0
9 BRS	L9	343	protease adj nexin\$12	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:09			0
10 BRS	L10	2155	antithrombin adj III	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:10			0

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(FILE 'HOME' ENTERED AT 07:20:19 ON 09 DEC 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA'  
ENTERED AT

07:21:46 ON 09 DEC 2002

L1 3355 S TFPI OR TFPI-2  
L2 1746 S KUNITZ (P) DOMAIN  
L3 354 S L1 (P) L2  
L4 4 S L3 (P) (CHIMERIC PROTEIN)  
L5 2 S L3 (P) (FUSION PROTEIN)  
L6 4 S L4 OR L5  
L7 4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)  
L8 2925 S HEPARIN BINDING DOMAIN  
L9 37901 S (PROTEASE NEXIN-1) OR (PROTEASE NEXIN-2) OR  
(ANTITHROMBIN III  
L10 12786 S (PLATELET FACTOR 4) OR (BOVINE PANCREATIC TRYPSIN  
INHIBITOR)  
L11 158 S L8 (P) (L9 OR L10)  
L12 0 S L7 (P) L11

FILE 'HOME' ENTERED AT 07:20:19 ON DEC 2002

	SINCE FILE	TOTAL
COST IN U.S. DOLLARS	ENTRY	SESSION
FULL ESTIMATED COST	0.63	0.63

FILE 'MEDLINE' ENTERED AT 07:21:46 ON 09 DEC 2002

FILE 'CAPLUS' ENTERED AT 07:21:46 ON 09 DEC 2002  
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FILE 'AGRICOLA' ENTERED AT 07:21:46 ON 09 DEC 2002

=> s TFPI or TFPI-2  
L1 3355 TFPI OR TFPI-2

=> s kunitz (p) domain  
L2 1746 KUNITZ (P) DOMAIN

=> s l1 (p) l2  
L3 354 L1 (P) L2

=> s l3 (p) (chimeric protein)  
L4 4 L3 (P) (CHIMERIC PROTEIN)

=> s l3 (p) (fusion protein)  
L5 2 L3 (P) (FUSION PROTEIN)

=> s l4 or l5  
L6 4 L4 OR L5

=> duplicate remove l6  
DUPLICATE PREFERENCE IS 'CAPLUS, BIOSIS'  
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n  
PROCESSING COMPLETED FOR L6  
L7 4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)

=> s heparin binding domain  
L8 2925 HEPARIN BINDING DOMAIN

=> s (protease nexin-1) or (protease nexin-2) or (antithrombin III) or (heparin cofactor II) or (p  
4 FILES SEARCHED...  
L9 37901 (PROTEASE NEXIN-1) OR (PROTEASE NEXIN-2) OR (ANTITHROMBIN III)  
OR (HEPARIN COFACTOR II) OR (PROTEIN C INHIBITOR)

=> s (platelet factor 4) or (bovine pancreatic trypsin inhibitor) or (ghilanten-related inhibitor)  
5 FILES SEARCHED...  
L10 12786 (PLATELET FACTOR 4) OR (BOVINE PANCREATIC TRYPSIN INHIBITOR) OR  
(GHILANTEN-RELATED INHIBITOR)

=> s L8 (p) (l9 or l10)  
L11 158 L8 (P) (L9 OR L10)

=> s l7 (p) l11  
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH  
FIELD CODE - 'AND' OPERATOR ASSUMED 'L72 (P) L65'  
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH  
FIELD CODE - 'AND' OPERATOR ASSUMED 'L78 (P) L68'  
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH

FIELD CODE - 'AND' OPERATOR ASSUMED 'L80 (P) L69'  
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH  
FIELD CODE - 'AND' OPERATOR ASSUMED 'L82 (P) L70'  
L12            0 L7 (P) L11

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L4            4 S L3 (P) (CHIMERIC PROTEIN)  
L5            2 S L3 (P) (FUSION PROTEIN)  
L6            4 S L4 OR L5  
L7            4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)  
L8            2925 S HEPARIN BINDING DOMAIN  
L9            37901 S (PROTEASE NEXIN-1) OR (PROTEASE NEXIN-2) OR (ANTITHROMBIN III  
L10           12786 S (PLATELET FACTOR 4) OR (BOVINE PANCREATIC TRYPSIN INHIBITOR)  
L11           158 S L8 (P) (L9 OR L10)  
L12           0 S L7 (P) L11

=> d 17 1-4 ibib abs

L7 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:340475 BIOSIS

DOCUMENT NUMBER: PREV200100340475

TITLE: Chimeric proteins.

AUTHOR(S): Innis, Michael A.; Creasey, Abba A.

ASSIGNEE: Chiron Corporation

PATENT INFORMATION: US 6174721 January 16, 2001

SOURCE: Official Gazette of the United States Patent and Trademark  
Office Patents, (Jan. 16, 2001) Vol. 1242, No. 3, pp. No  
Pagination. e-file.  
ISSN: 0098-1133.

DOCUMENT TYPE: Patent

LANGUAGE: English

AB \*\*\*Chimeric\*\*\* \*\*\*proteins\*\*\* possessing \*\*\*Kunitz\*\*\* -type  
\*\*\*domain\*\*\* 1 of \*\*\*TFPI\*\*\* - \*\*\*2\*\*\* and \*\*\*Kunitz\*\*\* -type  
\*\*\*domain\*\*\* 2 of \*\*\*TFPI\*\*\* are disclosed, as are muteins of  
\*\*\*TFPI\*\*\* and \*\*\*TFPI\*\*\* - \*\*\*2\*\*\*. Nucleic acid sequences,  
expression vectors and transformed host cells encoding and capable of  
producing the disclosed \*\*\*chimeric\*\*\* \*\*\*proteins\*\*\* and muteins  
are also disclosed. Finally, methods for prevention and treatment of  
septic shock using the \*\*\*chimeric\*\*\* \*\*\*proteins\*\*\* and muteins  
are disclosed.

L7 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:311733 BIOSIS

DOCUMENT NUMBER: PREV200100311733

TITLE: Inhibition of endotoxin-induced coagulation in rats by XK1,  
a potent and selective tissue factor-factor VIIa inhibitor.  
AUTHOR(S): Conricode, Kevin M. (1); LaChance, Rhonda M. (1); Girard,  
Thomas J. (1)

CORPORATE SOURCE: (1) Pharmacia Corporation, St. Louis, MO USA

SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 54a.  
print.  
Meeting Info.: 42nd Annual Meeting of the American Society  
of Hematology San Francisco, California, USA December  
01-05, 2000 American Society of Hematology  
. ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Sepsis is frequently complicated by disseminated intravascular coagulation  
(DIC) with associated consumption of blood coagulation factors. Animal  
model studies of endotoxin- and bacteria-induced DIC have implicated  
tissue factor (TF) as the trigger for activation of coagulation. We have  
tested the effectiveness of a highly potent and selective inhibitor of  
TF-factor VIIa in reducing endotoxin-induced DIC in rats. This unique

inhibitor, referred to here as XK1, is a \*\*\*chimeric\*\*\*  
 \*\*\*protein\*\*\* which consists of the gla \*\*\*domain\*\*\* -c containing  
 light chain of factor X linked to the first \*\*\*Kunitz\*\*\*  
 \*\*\*domain\*\*\* of \*\*\*TFPI\*\*\* (Science 148:1421-4). Endotoxin-induced  
 coagulation was evaluated by determining plasma thrombin-antithrombin  
 complex (TAT) levels following iv. injection of 0.3 mg/kg LPS into  
 anesthetized rats. In control (vehicle-infused) rats, TAT increased from  
 0.4 + 0.1 mug/l (mean + S.E.) at baseline to 8.9 + 0.9 mug/l at 120 min  
 after LPS injection and 19.2 + 1.8 mug/l at 180 min (n=17). Infusion of  
 XK1 at 15 mug/kg/min (started 30 min prior to and continued until 180 min  
 after LPS injection) reduced plasma TAT to 2.3 + 0.4 mug/l at 120 min and  
 13.5 + 2.7 mug/l at 180 min (n=7), while infusion at 60 mug/kg/min further  
 decreased TAT to 1.0 + 0.3 mug/l and 7.8 + 3.0 mug/l at 120 and 180 min,  
 respectively (n=5). Plasma XK1 levels reached approximately 4 mug/ml with  
 the low dose and 25 mug/ml, a concentration which prolongs the prothrombin  
 time of human plasma by more than 10-fold, with the high dose. The  
 consumption of plasma fibrinogen at 240 min after LPS injection was  
 attenuated by the high dose of XK1 (112 + 14 mg/dl versus 134 + 9 mg/dl  
 for control and high dose XK1 groups, respectively; n=4 in each group).  
 Blood loss following tail transection was also increased from 0.132 +  
 0.022 g with the vehicle (n=13) to 0.319 + 0.042 g with low dose XK1 (n=3)  
 and 0.538 + 0.084 g with high dose XK1 (n=4). We conclude that XK1 at  
 least partially reduces endotoxin-induced coagulation in rats. The  
 possible complete blockade of coagulation by very high doses of XK1 in  
 this model remains to be demonstrated.

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:695173 CAPLUS

DOCUMENT NUMBER: 132:175508

TITLE: Structural requirements for TFPI-mediated inhibition  
 of neointimal thickening after balloon injury in the  
 rat

AUTHOR(S): Han, Xin; Girard, Thomas J.; Baum, Pamela;  
 Abendschein, Dana R.; Broze, George J., Jr.

CORPORATE SOURCE: Division of Hematology/Oncology, Barnes-Jewish  
 Hospital at Washington University Medical Center, St.  
 Louis, MO, 63110, USA

SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology  
 (1999), 19(10), 2563-2567

CODEN: ATVBFA; ISSN: 1079-5642

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The intimal thickening that follows vascular injury is inhibited by  
 periprocedural tissue factor pathway inhibitor (TFPI) treatment in animal  
 models. TFPI is a multivalent Kunitz-type protease inhibitor that  
 inhibits factor Xa via its second Kunitz domain and the factor VIIa/tissue  
 factor (TF) complex via its first Kunitz domain. The basic C-terminus of  
 TFPI is required for the binding of TFPI to cell surfaces and cell-bound  
 TFPI mediates the internalization and degrdn. of factor X and the down  
 regulation of surface factor VIIa/TF activity. The C-terminus of TFPI is  
 also required for its reported direct inhibition of smooth muscle cell  
 proliferation in vitro. To examine the structural requirements for the  
 inhibition of neointimal formation by TFPI, several TFPI-related proteins  
 were tested in the rat carotid angioplasty model: (1) XK1, a hybrid  
 protein contg. the N-terminal portion of factor X and the first Kunitz  
 domain of TFPI that directly inhibits factor VIIa/TF; (2) TFPIWT, the  
 full-length TFPI mol. that inhibits factor Xa and factor VIIa/TF and binds  
 cell surfaces; (3) TFPIK361, an altered form of TFPI that inhibits factor  
 Xa, but not factor VIIa/TF, and binds cell surfaces; (4) TFPI13-161, a  
 truncated form of TFPI that inhibits factor VIIa/TF but interacts with  
 factor Xa poorly and does not bind to cell surfaces. Seven day infusions  
 of XK1, TFPIWT, and high levels of TFPIK361 begun the day before  
 balloon-induced vascular injury produced a significant redn. in the  
 intimal hyperplasia measured 28 days after angioplasty. The infusion of  
 high concns. of TFPI13-161 was ineffective in this model. These in vivo  
 results directly mirror the ability of each TFPI-related protein to  
 inhibit tissue thromboplastin-induced coagulation in rat plasma:  
 XK1.apprxeq.TFPIWT>TFPIK361>>TFPI13-161. The studies confirm the  
 important role of TF-mediated coagulation in the smooth muscle  
 proliferation and neointimal thickening that follows vascular injury and  
 suggest that the anticoagulant effect alone of TFPI and TFPI-related

proteins is sufficient to explain their therapeutic action.  
REFERENCE COUNT: 33 THE ARE 33 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 1996:295080 CAPLUS  
DOCUMENT NUMBER: 124:325361  
TITLE: Chimeric proteins and muteins of tissue factor pathway  
inhibitors TFPI and TFPI-2  
INVENTOR(S): Innis, Michael A.; Creasey, Alba A.  
PATENT ASSIGNEE(S): Chiron Corporation, USA  
SOURCE: PCT Int. Appl., 67 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604378	A2	19960215	WO 1995-US9464	19950725
WO 9604378	A3	19960314		
W: AU, CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5589359	A	19961231	US 1994-286521	19940805
US 5563123	A	19961008	US 1995-437841	19950509
US 5696088	A	19971209	US 1995-436175	19950509
CA 2196290	AA	19960215	CA 1995-2196290	19950725
AU 9531500	A1	19960304	AU 1995-31500	19950725
AU 710535	B2	19990923		
EP 776366	A1	19970604	EP 1995-927478	19950725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10503375	T2	19980331	JP 1995-506598	19950725
US 6174721	B1	20010116	US 1997-943682	19971014
PRIORITY APPLN. INFO.:			US 1994-286521	A 19940805
			US 1995-438184	B1 19950509
			WO 1995-US9464	W 19950725

AB \*\*\*Chimeric\*\*\* \*\*\*proteins\*\*\* possessing \*\*\*Kunitz\*\*\* -type  
\*\*\*domain\*\*\* 1 of \*\*\*TFPI\*\*\* - \*\*\*2\*\*\* and \*\*\*Kunitz\*\*\* -type  
\*\*\*domain\*\*\* 2 of \*\*\*TFPI\*\*\* are provided, as are muteins of  
\*\*\*TFPI\*\*\* and \*\*\*TFPI\*\*\* - \*\*\*2\*\*\* . Nucleic acid sequences,  
expression vectors, and transformed host cells encoding and capable of  
producing the disclosed \*\*\*chimeric\*\*\* \*\*\*proteins\*\*\* and muteins  
are also provided. \*\*\*Chimeric\*\*\* \*\*\*proteins\*\*\* were constructed  
with amino acid sequences capable of binding a cell surface component  
(glycosaminoglycan, heparin) such as peptide moieties from protease  
nexin-1, protease nexin-2, antithrombin III, heparin cofactor II, protein  
C inhibitor, platelet factor 4, bovine pancreatic trypsin inhibitor, and  
ghilanten-related inhibitors. The \*\*\*chimeric\*\*\* \*\*\*proteins\*\*\*  
are produced as yeast .alpha.-factor \*\*\*fusion\*\*\* \*\*\*proteins\*\*\*  
for secretion, or alternatively, may be expressed as a ubiquitin  
\*\*\*fusion\*\*\* \*\*\*protein\*\*\* . Potential sites for N-linked  
glycosylation within \*\*\*TFPI\*\*\* (Asn116.fwdarw.Gln, Asn227.fwdarw.Gln)  
are removed using overlapping PCR and mutations och1, mn1, and alg3 are  
introduced in transformed yeast cells to prevent the prodn. of  
.alpha.-1,6-polymannose terminal carbohydrate moieties in the chimeric  
products. Finally, methods for prevention and treatment of septic shock  
using the \*\*\*chimeric\*\*\* \*\*\*proteins\*\*\* and muteins are described.

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L5 2 S L3 (P) (FUSION PROTEIN)  
L6 4 S L4 OR L5

L7 4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)  
 L8 2925 S HEPARIN BINDING MAIN  
 L9 37901 S (PROTEASE NEXIN-1) OR (PROTEASE NEXIN-2) OR (ANTITHROMBIN III  
 L10 12786 S (PLATELET FACTOR 4) OR (BOVINE PANCREATIC TRYPSIN INHIBITOR)  
 L11 158 S L8 (P) (L9 OR L10)  
 L12 0 S L7 (P) L11

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COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
74.15	74.78

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-1.24	-1.24

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